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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,252	08/19/2004	Francois Romagne	INN-112	7415

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,252	ROMAGNE ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-50* is/are pending in the application.

4a) Of the above claim(s) *35-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 21-34, in the reply filed on 9 January 2006 is acknowledged. Because the election was made without traverse the restriction requirement is made FINAL. Applicants did not elect a species of synthetic activator; however in a telephone interview with Dr. F. C. Eisenschenk on 3 March 2006, applicants elected the species of phosphohalohydrin, specifically 3-(bromomethyl)-3-butanol-1-yl diphosphate (BrHPP). Claims 21-50 remain pending in the current application, with claims 35-50 being withdrawn from consideration as being directed to non-elected inventions. Claims 21-34 have been examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' claims are directed to a method for preparing a gamma delta T lymphocyte composition comprising culturing a biological preparation comprising at least 50 million mononuclear cells in the presence of a synthetic activator compound of gamma delta T lymphocytes and a cytokine.

Applicants fail to provide sufficient description of a representative number of 'synthetic activator compounds of gamma delta T lymphocytes' which can successfully be utilized in the claimed method, a representative number of species is required to claim the entire genus of 'synthetic activator compounds

of gamma delta T lymphocytes. In the instant case applicant has identified three distinct types of compounds which are considered synthetic activators of gamma delta T lymphocytes: phosphohalohydrin compounds, phosphoepoxide compounds, and bisphosphonate compounds, as well as several representative species of each. However, while applicant has described a sufficient number of representative species of phosphohalohydrins, phosphoepoxides and bisphosphonate compounds in order to claim those particular types of compounds as synthetic activators of gamma delta T lymphocytes for use in the present invention, such a listing is not sufficient to claim all synthetic activators of gamma delta T lymphocytes. In claiming *all* synthetic activators of gamma delta T lymphocytes one encompasses all compounds, known and yet to be discovered that are capable of activating gamma delta T lymphocytes. While applicants have identified structural and chemical properties common to each type of synthetic compound (phosphohalohydrins, phosphoepoxides and bisphosphonates), they have not identified such relevant characteristics shared by all currently known synthetic activators and which would be shared by all yet to be discovered synthetic activators, beyond the generic action (activation of gamma delta T lymphocytes), sufficient to show applicant was in possession of the claimed genus. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406.

Furthermore, applicant fails to provide sufficient description of a representative number of cytokine species which can successfully be used in the claimed method, a representative number of species is required to claim the entire genus of cytokines. Additionally, there is no disclosure of relevant, identifying characteristics, such as structure or other physical or chemical properties, or functional characteristics of suitable cytokines which make them appropriate for use in the currently claimed method, sufficient to show the applicant was in possession of the claimed genus. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. In the instance of chemical structures

(such as cytokines) one must define a compound by 'whatever characteristics sufficiently distinguish it'; while applicants have particularly pointed out that IL-2 and IL-15 are appropriate for use in the claimed method due to their ability to stimulate proliferation of gamma delta T lymphocytes, they have failed to describe the specific structure or action of IL-2 and IL-15 that cause the gamma delta T lymphocyte proliferation. Such a description of the relevant, active portion or characteristic of the cytokine is required to permit one of ordinary skill in the art to immediately envisage all suitable cytokines which can be successfully used in the claimed method. MPEP § 2163

Claims 21-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing a gamma delta T lymphocyte population from a peripheral blood cell preparation comprising gamma delta lymphocytes, does not reasonably provide enablement for preparing a gamma delta T lymphocyte population from any biological preparation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicants' method involves expansion of a gamma delta T lymphocyte population in a cell sample by culturing a cell sample, which initially contains a very low percentage of gamma delta T lymphocytes, in the presence of synthetic activators, namely BrHPP, and cytokines which are necessary for the growth and proliferation of gamma delta T lymphocytes. Therefore, because applicants' method relies on expanding an initial gamma delta T lymphocyte population, the cell sample used as the 'biological preparation' must contain at least some gamma delta T cells. In their examples, applicants use lymphocytes isolated from peripheral blood as the 'biological preparation;' the lymphocytes were isolated from whole blood by Ficoll gradient separation or by cytapheresis (See Spec, Pg. 20). Applicants provide no other source of 'biological preparations' suitable for their method.

The term 'biological preparation' goes well beyond the scope of the current invention; even biological preparations comprising mononuclear cells can read on almost any eukaryotic cell population. However, the current invention is limited to cell populations which initially comprise at least some gamma delta T lymphocytes, which clearly not all eukaryotic cell populations comprise, e.g. any biologically pure cell culture of any eukaryotic cell besides gamma delta T lymphocytes. Additionally, it is noted that while claims 22 and 23 limits the 'biological preparation' only whole blood, or fractions of blood comprising lymphocytes, are permissible for the claimed method, biological preparations consisting of plasma or serum do not comprise gamma delta T lymphocytes, which is required for successfully performing the claimed method. Therefore, applicants' method is limited to biological preparations that initially comprise at least some gamma delta T lymphocytes. Furthermore, while it may be argued that gamma delta T lymphocytes are present in a variety of tissues in the mammalian body, as they circulate throughout the body, particularly to the epithelial tissues, applicants have only provided guidance and teachings for use of cell samples obtained from peripheral blood comprising lymphocytes. Applicants have provided no guidance or teachings on how to identify and isolate other heterogeneous cell populations which contain gamma delta T lymphocytes in sufficient concentrations to successfully perform the claimed method. Thus applicants method is limited to preparing a gamma delta T lymphocyte composition from a peripheral blood sample comprising the lymphocyte fraction.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belmant et al (WO 00/12516 (French Language); US Patent 6,660,723, which is the US national stage application, is relied upon as a direct translation), in view of Garcia et al (Journal of Immunology, 1998) and Valeri (Blood Banking and the Use of Frozen Blood Products, 1976).

Applicants' claims are directed to a method for preparing a gamma delta T lymphocyte composition comprising culturing a biological preparation comprising at least 50 million mononuclear cells in the presence of a synthetic activator compound of gamma delta T lymphocytes and a cytokine. Claim 22 requires the biological preparation to be blood, plasma or serum sample; claim 23 requires the sample to be from cytapheresis. Claim 24 requires the biological preparation to comprise more than 10 x 10^7 cells. Claim 25 requires the biological preparation to have previously been frozen. Claim 26 requires the cells to be maintained at a concentration less than about 5 x 10^6 cells/mL during culturing. Claim 27 requires the cells to be cultured for greater than or equal to 10 days, claims 28 requires the culture period to be 10 to 25 days. Claims 29-31 require the synthetic activator to be BrHPP. Claim 32 requires the cytokine to be IL-2 or IL-15. Claim 33 requires the cytokine to be used at a concentration of about 150 U/mL to about 500 U/mL. Claim 34 requires the resulting gamma delta T lymphocyte population to comprise at least 80% gamma delta T lymphocytes and for the composition to comprise more than 100 million viable and functional gamma delta T cells.

Belmant et al teach a large variety of phosphohalohydrins as well as methods of using the phosphohalohydrins for gamma delta T lymphocyte activation (See Belmant et al, col. 2, ln 44-65). As one of the exemplary phosphohalohydrins Belmant et al teach 3-(bromomethyl)-3-butanol-1-yl-diphosphate (BrHPP) (See Belmant et al, col. 17, ln 30-60) (Claims 29-31).

Belmant et al also teach a method for activation of gamma delta T lymphocytes comprising contacting gamma delta T lymphocytes with a) one of their phosphohalohydrins; and b) interleukin-2 (IL-2). Belmant et al further teach the gamma delta T lymphocytes may be part of a peripheral blood sample

or blood extract (See Belmant et al, col. 11, ln 63-col. 12, ln 35 & claim 13) (Claims 22 & 32). Therefore, it is within the scope of Belmant et al to contact a peripheral blood sample with BrHPP and IL-2 in order to activate and expand the gamma delta T lymphocyte population present within the peripheral blood sample.

While Belmant et al merely teach 'contacting' the gamma delta T lymphocytes with the BrHPP and IL-2 in a medium (blood), instead of a specific 'culture' step, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to interpret the 'contacting' of Belmant et al as a culturing step. The method of Belmant et al is intended to activate and expand gamma delta T lymphocytes for a variety of therapeutic uses; one of ordinary skill in the art would recognize that for activation of cells *in vitro* cells must be cultured for a suitable time period in the presence of the stimulus in order to achieve the desired result.

Regarding the duration of the culture period, the cell density before and during culture, and the concentration of the activator compounds (BrHPP and IL-2), in the field of cell culture such parameters are generally recognized to be result effective variables that would directly effect the final gamma delta T lymphocyte population within the sample; such parameters would routinely be optimized by one of ordinary skill in the art. The length of time the cells are maintained in culture directly affects the final gamma delta T lymphocyte concentration within the sample. A longer culture period would ensure a higher number and percentage of gamma delta T lymphocytes, as the gamma delta T lymphocytes would have been exposed to the activator compounds for a greater length of time. One of ordinary skill in the art would have been motivated to manipulate the length of the culture based on the desired proportion of gamma delta T lymphocytes in the sample. For example, a longer culture period of 2-3 weeks would allow for a greater proportion of gamma delta T lymphocytes, which may be desirable for *in vitro* studies, where a more pure population of gamma delta T lymphocytes are desired; alternatively a shorter culture period of several days to 1 or 2 weeks would be desirable when a lower proportion of gamma delta T

lymphocytes are required, which may be desired for reinfusion of the cells into a subject, or merely to save time and energy (Claims 27 & 28). The cell density of the initial cell culture, as well as the density throughout the culture period, directly affect the cells' ability to grow and divide; thus it would be well within the purview of one of ordinary skill in the art to initiate and maintain the culture at appropriate cell concentrations for the needs of the culture; the exact concentrations may vary based on how often the cell are passaged and how long the culture is to be maintained (Claims 21, 24 & 26). Finally, the concentration of the activator compounds, both BrHPP and IL-2, would also directly effect the rate of proliferation and expansion of the gamma delta T lymphocytes in the culture. For example, Belmant et al teach the concentration of the IL-2 to be "in a proportion suitable to bring about lymphocyte growth" (See Belmant et al, col. 12, ln 5-7); therefore, while applicant specifically claims a cytokine concentration in the range of 150 U/mL to 500 U/mL, manipulation and optimization within this range would be well within the purview of one of ordinary skill in the art, again based on the desired activation rate of the cells as well as how often the cells are passaged (Claim 33). Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical or produces unexpected results. Where the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation, See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It then naturally follows that because all of the above discussed variables directly effect the final gamma delta T lymphocyte cell count and concentration in the final composition, it would have been within the purview of one of ordinary skill in the art to optimize any and each of the variables so as to produce a composition with any desired cell concentration and cell count, including at least 80% gamma delta T lymphocytes and at least 100 million cells. One would have motivated to create a large cell population with a substantially high proportion of gamma delta T lymphocytes for use in *in vitro* studies on gamma delta T lymphocytes, or for reinfusion of the cells *in vivo* for treatment of various diseases, as

disclosed by Belmant et al. One would have expected success optimizing the cell count and gamma delta T lymphocyte cell proportion because these variables are directly controlled by the culture steps and parameters discussed above; it would be well within the purview of one of ordinary skill in the art to optimize the culture conditions (extend culture time period, adjust time between passages, adjust concentration of activation agents) in order to create a gamma delta T lymphocyte composition with the desired cell numbers and proportions (Claim 34).

Still further, regarding the cytokines used in the experiments of Belmant et al, while Belmant et al added IL-2 to their media, it would further have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively add IL-15 to the culture medium. In support see Garcia et al; Garcia et al teach that specific cytokines, including IL-2 and IL-15 are known to enhance gamma delta T lymphocyte activation in the presence of an activator of gamma delta T cells (See Garcia et al, Pg. 4324 & Fig. 2). Garcia et al unexpectedly found IL-15 to be a more potent induces of gamma delta T cell proliferation than IL-2 (See Garcia et al, Pg. 4324, col. 2). Therefore, it would have been well within the purview of one of ordinary skill in the art to alternatively utilize IL-15 in place of, or in addition to, the IL-2 used by Belmant et al (Claims 1 & 32). One of ordinary skill in the art would be motivated to substitute IL-15 for IL-2 in the method of Belmant et al because Garcia et al teach IL-15 is more potent than IL-2 in enhancing gamma delta T cell proliferation. One would expect success based on the experimental findings of Garcia et al, which show successful activation and proliferation of gamma delta T cells in the presence of IL-15 and an activator compound. Regarding the concentration of IL-15 used, Garcia et al use of up to 100 ng/mL of IL-15, but report the effect of IL-15 on gamma delta T cell proliferation was dose dependent (See Garcia et al, Pg. 4324, col. 2). Therefore, while applicant specifically claims a cytokine concentration in the range of 150 U/mL to 500 U/mL, manipulation and optimization within this range would be well within the purview of one of ordinary skill in the art, again based on the desired activation rate of the cells as well as how often the cells are passaged (Claim 33).

Finally, while Belmant et al teaches the gamma delta T lymphocytes can be from a blood sample or blood extract, they do not specifically teach separating whole blood by cytapheresis prior to the culture method described above, nor do they teach using previous frozen samples of blood. However, at the time the invention was made it would have been well within the purview of one of ordinary skill in the art to obtain a blood sample at a first point in time, separate the whole blood sample by cytapheresis into individual components, freeze the individual components by appropriate means known in the art, and then at later time, thaw the desired platelet component for use in the method of Belmant et al (Claims 23 and 25). In support see Valeri; Valeri teaches the basic protocols for obtaining, separating and storing blood. Valeri teaches cytapheresis allows separation of specific components of blood from whole blood (See Valeri, Pg. 1, col. 1). Separating the platelets via 'plateletpheresis' removes the majority of red blood cells and plasma components, thereby increasing the proportion of gamma delta T lymphocytes present in the initial cell sample, which is desirable in the method of Belmant et al, as it would ensure a higher proportion of gamma delta T lymphocytes for culture and expansion, resulting in a greater end cell count. Additionally, Valeri teaches methods for frozen storage of separated platelets (See Valeri, Pg 297), which is desirable when the blood sample must be stored for a period of greater than 4 hours prior to use in the method of Belmant et al (See Valeri, Pg. 6, col. 1). One would expect success separating the desired platelet component via cytapheresis and storing the separated components in a frozen state for future use, because such methods and procedures are common in the art of hematology, as demonstrated by the teachings of Valeri.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Espinosa et al (Journal of Biological Chemistry, 2001), in view of Garcia et al (Journal of Immunology, 1998) and Valeri (Blood Banking and the Use of Frozen Blood Products, 1976).

Applicants' claims are directed to a method for preparing a gamma delta T lymphocyte composition comprising culturing a biological preparation comprising at least 50 million mononuclear cells in the presence of a synthetic activator compound of gamma delta T lymphocytes and a cytokine. Claim 22 requires the biological preparation to be blood, plasma or serum sample; claim 23 requires the sample to be from cytapheresis. Claim 24 requires the biological preparation to comprise more than 10 x 10^7 cells. Claim 25 requires the biological preparation to have previously been frozen. Claim 26 requires the cells to be maintained at a concentration less than about 5 x 10^6 cells/mL during culturing. Claim 27 requires the cells to be cultured for greater than or equal to 10 days, claims 28 requires the culture period to be 10 to 25 days. Claims 29-31 require the synthetic activator to be BrHPP. Claim 32 requires the cytokine to be IL-2 or IL-15. Claim 33 requires the cytokine to be used at a concentration of about 150 U/mL to about 500 U/mL. Claim 34 requires the resulting gamma delta T lymphocyte population to comprise at least 80% gamma delta T lymphocytes and for the composition to comprise more than 100 million viable and functional gamma delta T cells.

Espinosa et al sought to identify a synthetic activator of gamma delta T lymphocytes that has comparable immunostimulatory activity as natural phosphoantigens; Espinosa et al discovered BrHPP enabled immunostimulation of human gamma delta T lymphocytes (See Espinosa et al, abstract).

Espinosa et al first perform a control run using the known, natural phosphoantigen 3-formyl-1-butyl-pyrophosphate (3fbPP); peripheral blood lymphocytes were cultured at an initial concentration of 10^6 cells/mL in the presence of 10nM 3fbPP and 100 U/mL IL-2 for a 15 day period (See Espinosa et al, Pg. 18338, col. 1). Espinosa et al report significant expansion of the gamma delta T lymphocytes,

including compositions comprising greater than 95% TCR Vδ2 positive cells (gamma delta T lymphocytes) (See Espinosa et al, Pg. 18338, col. 2).

Espinosa et al then perform an experimental run using several different concentrations (12.5, 25, 100 nM) of BrHPP as the activator instead of the natural 3fbPP (See Espinosa et al, Pg. 18340, col. 1-2 & Fig. 4). Espinosa et al do not specifically describe the culture conditions of the experimental run, while they do state that peripheral blood cells were used, they are silent on the initial cell count, the length of the culture period, and whether or not IL-2 was added to the culture. However, it appears the culture conditions for the experimental run were identical to the conditions of the control run: 10^6 cells/mL were present in initial culture as well as 100 U/mL of IL-2, and the culture was maintained for 15 days. One of ordinary skill in the art would assume that for results to be comparable between the immunostimulatory activity of the 3fbPP and BrHPP, the culture conditions were identical. Therefore, in the absence of evidence to the contrary, it is assumed Espinosa et al performed a method for activation of a gamma delta T lymphocyte composition comprising culturing peripheral blood lymphocytes (PBL) in the presence of BrHPP (a synthetic activator of gamma delta T lymphocytes) and IL-2.

However, even if the culture conditions described for the control run were not duplicated in the experimental run, it would have been well within the purview of one of ordinary skill in the art to optimize the duration of the culture period, the cell density before and during culture, and the concentration of the activator compounds (BrHPP and IL-2), in the field of cell culture such parameters are generally recognized to be result effective variables that would directly effect the final gamma delta T lymphocyte population within the sample; such parameters would routinely be optimized by one of ordinary skill in the art. The length of time the cells are maintained in culture directly affects the final gamma delta T lymphocyte concentration within the sample. A longer culture period would ensure a higher number and percentage of gamma delta T lymphocytes, as the gamma delta T lymphocytes would have been exposed to the activator compounds for a greater length of time. One of ordinary skill in the

art would have been motivated to manipulate the length of the culture based on the desired proportion of gamma delta T lymphocytes in the sample. For example, a longer culture period of 2-3 weeks would allow for a greater proportion of gamma delta T lymphocytes, which may be desirable for *in vitro* studies, where a more pure population of gamma delta T lymphocytes are desired; alternatively a shorter culture period of several days to 1 or 2 weeks would be desirable when a lower proportion of gamma delta T lymphocytes are required, which may be desired for reinfusion of the cells into a subject, or merely to save time and energy (Claims 27 & 28). The cell density of the initial cell culture, as well as the density throughout the culture period, directly affect the cells' ability to grow and divide; thus it would be well within the purview of one of ordinary skill in the art to initiate and maintain the culture at appropriate cell concentrations for the needs of the culture; the exact concentrations may vary based on how often the cell are passaged and how long the culture is to be maintained (Claims 21, 24 & 26). Finally, the concentration of the activator compounds, both BrHPP and IL-2, would also directly effect the rate of proliferation and expansion of the gamma delta T lymphocytes in the culture. For example, Espinosa et al teach the concentration of the IL-2 to be 100 U/mL (See Espinosa et al, Pg. 18338, col. 1); however, while applicant specifically claims a cytokine concentration in the range of 150 U/mL to 500 U/mL, manipulation and optimization within this range would be well within the purview of one of ordinary skill in the art, again based on the desired activation rate of the cells as well as how often the cells are passaged (Claim 33). Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical or produces unexpected results. Where the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation, See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It then naturally follows that because all of the above discussed variables directly effect the final gamma delta T lymphocyte cell count and concentration in the final composition, it would have been

within the purview of one of ordinary skill in the art to optimize any and each of the variables so as to produce a composition with any desired cell concentration and cell count, including at least 80% gamma delta T lymphocytes and at least 100 million cells. In the instant reference Espinosa et al report a final gamma delta T lymphocyte population which comprises approximately 63% of total lymphocytes (See Espinosa et al, Fig. 4a); alternatively, Espinosa et al teach the concentration of BrHPP directly effects the final gamma delta T lymphocyte count (See Pg. 18340, col. 2 & Fig. 4B). Thus one would have expected success optimizing the cell count and gamma delta T lymphocyte cell proportion because these variables are directly controlled by the culture steps and parameters discussed above, particularly the concentration of BrHPP; it would be well within the purview of one of ordinary skill in the art to optimize the culture conditions (extend culture time period, adjust time between passages, adjust concentration of activation agents) in order to create a gamma delta T lymphocyte composition with the desired cell numbers and proportions (Claim 34).

Still further, regarding the cytokines used in the experiments of Espinosa et al, while Espinosa et al added IL-2 to their media, it would further have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively add IL-15 to the culture medium. In support see Garcia et al; Garcia et al teach that specific cytokines, including IL-2 and IL-15 are known to enhance gamma delta T lymphocyte activation in the presence of an activator of gamma delta T cells (See Garcia et al, Pg. 4324 & Fig. 2). Garcia et al unexpectedly found IL-15 to be a more potent induces of gamma delta T cell proliferation than IL-2 (See Garcia et al, Pg. 4324, col. 2). Therefore, it would have been well within the purview of one of ordinary skill in the art to alternatively utilize IL-15 in place of, or in addition to, the IL-2 used by Espinosa et al (Claims 1 & 32). One of ordinary skill in the art would be motivated to substitute IL-15 for IL-2 in the method of Espinosa et al because Garcia et al teach IL-15 is more potent than IL-2 in enhancing gamma delta T cell proliferation. One would expect success based on the experimental findings of Garcia et al, which show successful activation and proliferation of gamma delta

T cells in the presence of IL-15 and an activator compound. Regarding the concentration of IL-15 used, Garcia et al use of up to 100 ng/mL of IL-15, but report the effect of IL-15 on gamma delta T cell proliferation was dose dependent (See Garcia et al, Pg. 4324, col. 2). Therefore, as discussed above, while applicant specifically claims a cytokine concentration in the range of 150 U/mL to 500 U/mL, manipulation and optimization within this range would be well within the purview of one of ordinary skill in the art based on the desired activation and proliferation rate of the cells as well as how often the cells are passaged (Claim 33).

Finally, while Espinosa et al teach use of peripheral blood lymphocytes, they do not specifically teach separating whole blood by cytapheresis prior to the culture method described above, nor do they teach using previous frozen samples of blood. However, at the time the invention was made it would have been well within the purview of one of ordinary skill in the art to obtain a blood sample at a first point in time, separate the whole blood sample by cytapheresis into individual components, freeze the individual components by appropriate means known in the art, and then at later time, thaw the desired platelet component for use in the method of Espinosa et al (Claims 23 and 25). In support see Valeri; Valeri teaches the basic protocols for obtaining, separating and storing blood. Valeri teaches cytapheresis allows separation of specific components of blood from whole blood (See Valeri, Pg. 1, col. 1). Separating the platelets via 'plateletpheresis' removes the majority of red blood cells and plasma components, thereby increasing the proportion of gamma delta T lymphocytes present in the initial cell sample, which is desirable in the method of Espinosa et al, as it would ensure a higher proportion of gamma delta T lymphocytes for culture and expansion, resulting in a greater end cell count. Additionally, Valeri teaches methods for frozen storage of separated platelets (See Valeri, Pg 297), which is desirable when the blood sample must be stored for a period of greater than 4 hours prior to use in the method of Espinosa et al (See Valeri, Pg. 6, col. 1). One would expect success separating the desired platelet component via cytapheresis and storing the separated components in a frozen state for future use, because

such methods and procedures are common in the art of hematology, as demonstrated by the teachings of Valeri.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 80 and 100 of copending Application No. 10/537,394. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claimed in copending application 10/537,394 describes substantially the same method of expanding a gamma delta T lymphocyte population through use of a synthetic activator and a cytokine, particularly IL-2, as is currently claimed. The difference between the two applications is that the current method states "culturing a biological preparation" in the presence of the activator and cytokine, which implies *in vitro*, whereas the copending application requires injection of the activator and cytokine for

activation and stimulation of the cells *in vivo*; such a difference is not found to be patentably distinct because both methods rely on the ability of the synthetic activator and cytokine to stimulate activation and proliferation of gamma delta T lymphocytes, whether the cells are *in vitro* or *in vivo* does not appear to be critical.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER